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# Rat Data Only
library(gdata)
library(gmodels)
library(stats)

dta <- read.xls("PC_Data_rat.xls", sheet=1, skip=0)
colnames(dta) <- c("Drug","Tissue","Species","logP","logPSource","logMA",
  "pKa","ABN","fu","pHtissue","V","f_interstium",
  "F_vasc","f_Water","f_TotalLipid","f_Protein",
  "f_NeutralLipid","f_Phospholipid","f_AcidicPL","Exp_PC",
  "ExpPC_Source")

## alpha is the ratio between the distribution coefficient D of the
## totally charged species at a given pH and D_0 is that of the neutral form:
alpha <- 0.001

## D corresponds to the distribution coefficient at physiological pH and is
## to be used as the neutral lipid:water partition coefficient Kn_L:
## logD_used <- ifelse(dta$logPSource==7,dta$logP,ifelse(dta$ABN== "N",dta$logP,
## log10(10^(dta$logP)*((1-alpha)/(1+10^((1-2*(dta$ABN=="B"))*(dta$pHtissue-dta$pKa))) + alpha)))

logD_used <- ifelse(dta$logPSource==11,dta$logP,ifelse(dta$ABN== "N",dta$logP,
  log10(10^(dta$logP)*((1-alpha)/(1+10^((1-2*(dta$ABN=="B"))*(dta$pHtissue-dta$pKa))) + alpha)))
D <- 10^(logD_used)

## MA_n (D_pl:w) (sometimes known as "membrane affinity") determined with
## phosphatidylcholine should be used as the neutral phospholipid:water partition
## coefficient Kn_PL; if logMA not available , use logP as an estimate (see Schmitt) :
MA_n <- ifelse(dta$logMA=="",10^(dta$logP),10^(dta$logMA))

#MA_n <- 10^(dta$logMA)

## MA_c represents the acidic phospholipid:water partition coefficient Ka_PL
## (differs from formula used in Excel spreadsheet)
MA_c <- ifelse(dta$ABN=="N",MA_n, (dta$ABN=="A")*MA_n*(1/(1+10^(dta$pHtissue-dta$pKa))+20
  *(1-(1/(1+10^(dta$pHtissue-dta$pKa))))+(dta$ABN=="B")*MA_n
  *(1/(1+10^(dta$pKa-dta$pHtissue))+0.05*(1-(1/(1+10^(dta$pKa-dta$pHtissue)))))))

## Correlation function for protein:water partition coefficient in terms of MA_n (Kn_PL):
K_prot <- 0.163 + 0.0221*MA_n
## Note: K_prot <- ((0.81 + 0.11*MA_n)/24.92)*5 used in Schmitt's Excel spreadsheet

## Rescaling so that values for total lipid and protein fractions are in terms of
## cellular volume; water fraction was reduced by the fraction of extracellular water
## (94% of the interstitial space) and all values were divided by the fraction of the
## cellular space:
f_int_corr <- dta$f_interstium/(1-dta$F_vasc)

f_water_Int <- dta$f_Water - 0.94*dta$f_interstium

F_W <- f_water_Int/(1-dta$f_interstium)

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F_nL <- (dta$f_TotalLipid*dta$f_NeutralLipid)/(1-dta$f_interstium)

F_nPL <- (dta$f_TotalLipid*dta$f_Phospholipid*(1-dta$f_AcidicPL))/(1-dta$f_interstium)

F_aPL <- (dta$f_TotalLipid*dta$f_Phospholipid*dta$f_AcidicPL)/(1-dta$f_interstium)

F_P <- dta$f_Protein/(1-dta$f_interstium)

## K_int corresponds to unbound fraction in interstitial space 1/f_u^{int} under the
## assumptions that the ratio F_p^{int}/F_p^{pl} typically has a value of 0.37 and
## the water fractions are assumed to be virtually equal
K_int <- 0.935 + 0.37*(1/dta$fu - 0.935)
## Note: 0.935 + (0.0252/0.068)*(1/dta$fu - 0.935) used in Schmitt's Excel spreadsheet

## Kappa_{A:B}, the ratio between the unbound concentration in two compartments A and B
## with pH_A != pH_B which accounts for the influence of pH gradients, is given by K_AB:
K_AB <- ((1-alpha)/(1+10^{((1-2*(dta$ABN=="B"))*(dta$pKa-7.4)))}) + alpha)/((1-alpha)/(1+10^{((1-
2*(dta$ABN=="B"))
*(dta$pKa-dta$pHtissue)))}) + alpha)

## 1/f_u^{cell}, where f_u^{cell} is the unbound fraction in cellular space:
K_cell <- F_W + D*F_nL + MA_n*F_nPL + MA_c*F_aPL + K_prot*F_P

## Equilibrium tissue:plasma and blood cell:plasma partition coefficients in terms
## of unbound fractions:
dta$Pred_PC <- dta$fu*(dta$f_interstium*K_int + K_AB*(1-dta$f_interstium)*K_cell)

## Regression corrected predictions
## Adipose PC
adipose.data <- subset(dta,Tissue=="Adipose")
adipose.data$regressPC <- 0.46222*adipose.data$Pred_PC

## Brain PC
brain.data <- subset(dta,Tissue=="Brain")
brain.data$regressPC <- brain.data$Pred_PC

## Bone PC
bone.data <- subset(dta,Tissue=="Bone")
bone.data$regressPC <- bone.data$Pred_PC + 0.55791

## Gut PC
gut.data <- subset(dta,Tissue=="Gut")
gut.data$regressPC <- 0.49591*gut.data$Pred_PC + 0.35056

## Heart PC
heart.data <- subset(dta,Tissue=="Heart")
heart.data$regressPC <- heart.data$Pred_PC

## Kidney PC
kidney.data <- subset(dta,Tissue=="Kidney")
kidney.data$regressPC <- 0.63812*kidney.data$Pred_PC + 0.61411

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## Liver PC
liver.data <- subset(dta,Tissue=="Liver")
liver.data$regressPC <- liver.data$Pred_PC + 0.37409

## Lung PC
lung.data <- subset(dta,Tissue=="Lung")
lung.data$regressPC <- lung.data$Pred_PC + 0.52108

## Muscle PC
muscle.data <- subset(dta,Tissue=="Muscle")
muscle.data$regressPC <- muscle.data$Pred_PC + 0.22873

## Skin PC
skin.data <- subset(dta,Tissue=="Skin")
skin.data$regressPC <- 0.42136*skin.data$Pred_PC

## Spleen PC
spleen.data <- subset(dta,Tissue=="Spleen")
spleen.data$regressPC <- spleen.data$Pred_PC

## Testis PC
testis.data <- subset(dta,Tissue=="Testis")
testis.data$regressPC <- testis.data$Pred_PC + 0.59415

## Thymus PC
thymus.data <- subset(dta,Tissue=="Thymus")
thymus.data$regressPC <- thymus.data$Pred_PC + 0.8962
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